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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,951	09/18/2003	James McSwiggen	MBHB02-742-F (400.131)	8325
20306	7590	10/19/2005	EXAMINER	
MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP 300 S. WACKER DRIVE 32ND FLOOR CHICAGO, IL 60606			BOWMAN, AMY HUDSON	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/665,951	MCSWIGGEN ET AL.
	Examiner Amy H. Bowman	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 2 August 2005.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 36-56 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 36-56 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 18 September 2003 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date 7/22/04.

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

Applicant's cancellation of the pending claims and addition of new claims 36-56 in the amendment filed 8/2/2005 have obviated all previous rejections of record mailed 5/27/05.

Claim Objections

Claims 37, 38, 40, and 56 are objected to because of the following informalities: The claims read, "...wherein said the double stranded..." It appears that the word "the" should be removed from each claim. Appropriate correction is required.

Claim 36 reads, "...with the RNA encoded by VEGFr1 gene..." It appears that the word "the" or "said" should be inserted between by and VEGFr1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to a method of cleaving RNA encoded by a mammalian VEGFr1 gene.

At the outset, it is noted that the claims do not recite a specific target nucleotide sequence by SEQ ID NO, but rather refer to the broad genus of VEGFr1 sequences.

The claims encompass a method comprising contacting a double stranded nucleic acid molecule with RNA encoded by a VEGFr1 gene, as well as encompass targeting any VEGFr1 homolog or allele from any mammalian species known or yet to be discovered of VEGFr1, as well as DNA genomic fragments, splice variants or fragments that retain VEGFr1-like activity. Although the specification discloses double stranded nucleic acid sequences having complementarity to a VEGFr1 sequence, the specification does not describe such molecules directed to any other species of VEGFr1 to describe the instantly claimed genus of any double stranded nucleic acid targeted to any mammalian VEGFr1 gene. Each of the instantly disclosed double stranded molecules is targeted to a single sequence, although the claims are drawn to any mammalian VEGFr1 sequence. One of ordinary skill in the art could not make such oligos to any mammalian VEGFr1 gene without knowledge of the sequence. Given the breadth of sequences embraced in the instantly claimed genus, one could not envision the member oligonucleotides that target such a broad genus and the skilled artisan would recognize that the applicant was in possession of the claimed genus at the time of filing.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date of the instant claims is determined to be that of PCT/US03/05022, which has an effective filing date of 2/20/2003. The instant claims of application 10/665,951 do not receive the benefit of any of the earlier filed priority documents because none of the documents teach methods of targeting VEGFr1 with 19-29 nucleotide dsRNA molecules. Thus, the instant claims are accorded an effective filing date of 2/20/03.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 36 and 38-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Lockridge et al. (US 2003/0216335 A1).

The instant invention is drawn to a method of cleaving RNA encoded by a mammalian VEGFr1 gene comprising contacting a double stranded nucleic acid molecule with the RNA encoded by the VEGFr1 gene under conditions suitable for the cleavage of RNA, wherein each strand comprises 19-29 nucleotides and one or more chemical modifications, and one of the strands is complementary to RNA encoded by mammalian VEGFr1 gene and the other strand is complementary to the first strand. The invention is drawn to modifications to the dsRNA molecule, as well as the incorporation of linkers and terminal cap moieties.

Lockridge et al. teach methods of cleaving RNA encoded by VEGFr1 via contact with a siRNA molecule, wherein each strand of the siRNA molecule is 15-50 nucleotides in length. Lockridge et al. teach that each strand is about 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 nucleotides in length. One strand of the siRNA is complementary to RNA of a VEGFr1 gene, and the other strand is complementary to the first strand. Lockridge et al. teach an embodiment wherein the siRNA molecule comprises a double stranded RNA wherein both strands of the RNA are connected by a non-nucleotide or polynucleotide linker (see page 4). Lockridge et al. teach that preferably the nucleic acid molecule is modified extensively to enhance stability by modification with nuclease resistant groups, for example 2'-amino, 2'-fluoro, 2'-O-

methyl, or 2'-H groups (see page 16 for example). Lockridge et al. teach terminal cap moieties, for example a deoxyabasic moiety, at the 5'-end, 3'-end, or both (see page 4). Lockridge et al. teach an embodiment wherein the siRNA molecule comprises an inverted abasic moiety, as well as phosphorothioate linkages (see page 5).

Therefore, the instant invention is anticipated by Lockridge et al.

Claims 36 and 38-40, 44, 47, 48, 50 and 52 are rejected under 35 U.S.C. 102 (a) or (e) as being anticipated by Escobedo et al. (WO 02/096927 A2).

The instant invention is drawn to a method of cleaving RNA encoded by a mammalian VEGFr1 gene comprising contacting a double stranded nucleic acid molecule with the RNA encoded by the VEGFr1 gene under conditions suitable for the cleavage of RNA, wherein each strand comprises 19-29 nucleotides and one or more chemical modifications, and one of the strands is complementary to RNA encoded by mammalian VEGFr1 gene and the other strand is complementary to the first strand. The invention is drawn to modifications to the dsRNA molecule.

Escobedo et al. teach methods of reducing VEGFr1 expression or activity in a cell comprising contacting the cell with a nucleic acid molecule of the invention that modulates expression of VEGFr1 under conditions suitable for reduction (see page 11). The nucleic acid molecules taught by Escobedo et al. include dsRNA and siRNA duplexes. Each strand of the siRNA molecule is about 14 to about 50 nucleotides in length. Escobedo et al. teach that each strand is about 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 nucleotides in length (see page 10). Escobedo et al. teach

an embodiment wherein the nucleic acid molecule comprises a cap structure, for example a deoxyabasic derivative, at the 5'-end, 3'-end, or both. Escobedo et al. teach an embodiment wherein the nucleic acid molecule comprises at least ten 2'-O-methyl modifications, an inverted abasic moiety at the 3' end, or phosphorothioate linkages on at least three of the 5' terminal nucleotides (see page 13).

Therefore, the instant invention is anticipated by Escobedo et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 36-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tolentino et al. (US 2004/0018176 A1), in view of Pavco et al. (US 6,346,398 B1), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, pp. 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), and Cook et al. (US 5,587,471).

The instant invention is drawn to a method of cleaving RNA encoded by a mammalian VEGFr1 gene comprising contacting a double stranded nucleic acid molecule with the RNA encoded by the VEGFr1 gene under conditions suitable for the cleavage of RNA, wherein each strand comprises 19-29 nucleotides and one or more chemical modifications, and one of the strands is complementary to RNA encoded by

mammalian VEGFr1 gene and the other strand is complementary to the first strand.

The invention is drawn to modifications to the dsRNA molecule, linkers, terminal cap moieties, and 3' overhangs.

Tolentino et al. teach a method of inhibiting expression of human VEGF mRNA or human Flt-1 mRNA (which is an alternative name for VEGFr1), comprising administering an effective amount of siRNA comprising a sense and an antisense strand, wherein the sense and antisense strands form a duplex, and wherein the sense strand comprises a nucleotide sequence identical to the target sequence of about 19 to about 25 contiguous nucleotides (see claim 32). Tolentino et al. directly suggest modification to the siRNA duplex to make the siRNA resistant to nuclease degradation (see page 3). Tolentino et al. teach that one or both strands of the siRNA duplex can comprise a 3' overhang of at least one unpaired nucleotide, wherein the overhangs are 2'-deoxy-thymidines.

Tolentino et al. do not teach for each strand of the dsRNA molecule to comprise one or more chemical modifications. Tolentino et al. do not teach double stranded nucleic acid molecules that do not comprise ribonucleotides. Tolentino et al. do not teach linkers or the specific chemical modifications claimed.

Pavco et al. teach hammerhead ribozymes and antisense oligonucleotides targeted to flt-1. Pavco et al. teach chemical modifications including 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose. Pavco et al. teach that flt-1 is one of the most abundant VEGF receptors and that VEGF expression has been associated with several pathological states such as tumor angiogenesis and

rheumatoid arthritis. Pavco et al. teach that targeting and inhibiting flt-1 would beneficially decrease VEGF expression since VEGF exerts its influence by binding to cell surface receptors.

Elbashir et al. teach dsRNA duplexes 21-23 nucleotides in length with 2 nt 3' overhangs. Elbashir et al. teach 2'-deoxy and 2'-O-methyl modifications to one or both strands. Elbashir et al. teach that modifications are tolerated depending on the location in the duplex. Elbashir et al. teach that substitution of the 2 nt 3' overhangs by 2'-deoxynucleotides had no effect and even the replacement by two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Elbashir et al. teach complete substitution of one or both strands of the siRNA duplex, wherein the completely substituted duplex is considered to comprise no ribonucleotides.

Parrish et al. teach 26 bp siRNA duplexes that mediate RNAi. Parrish et al. teach modified double stranded siNA molecules comprising a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence. One or both strands comprise modifications. Each strand of the siNA molecules taught by Parrish et al. comprises 19 to 29 nucleotides, more specifically 26 nucleotides. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the interference process (see summary). Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand (see figure 5).

Matulic-Adamic et al. teach chemically modified ribozymes. The ribozymes taught by Matulic-Adamic et al. comprise ribonucleotides and cleave other separate RNA molecules in a nucleotide base sequence-specific manner. Such enzymatic RNA molecules are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. The modifications can be in one or both of the strands. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, Cl and F are representative halogens (see column 3, for example). Matulic-Adamic et al. teach the usage of polynucleotide or non-nucleotide linkers (see description of figure 3).

Cook et al. teach various conjugates and modifications that can be incorporated into oligonucleotides to improve the pharmacokinetic properties of an oligonucleotide, including glyceryl (see columns 2 and 3).

Tolentino et al. teach targeting siRNA duplexes targeted to Flt-1 mRNA and specifically suggest modification of the duplexes for resistance to nuclease degradation. Even without the Tolentino et al. art, the invention is still considered obvious in view of

the antisense art that teaches targeting the same gene for sequence specific inhibition of gene expression. Pavco et al. teach targeting the same gene with ribozymes and antisense oligonucleotides, as well as teach modifications to such structures.

Therefore, in absence of the Tolentino et al. art, it would have been obvious to design a siRNA to fit-1 since ribozymes and antisense oligos had been targeted to the same gene to decrease VEGF expression. Furthermore, it would have been obvious to modify the dsRNA duplexes with 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose, as taught by Pavco et al., 2'-deoxy and 2'-O-methyl modifications to one or both strands, as well as 3' overhangs of 2'-deoxy-thymidines, as taught by Elbashir et al., 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al., phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications, 2'-deoxy-2'-halogen nucleotides (wherein Br, CL and F are representative halogens), as well as to incorporate polynucleotide or non-nucleotide linkers, as taught by Matulic-Adamic et al., and glyceryl modifications, as taught by Cook et al.

One would have been motivated to incorporate each of the above mentioned modifications, since each of the modifications were known to enhance the activity of sequence specific inhibitors of target gene expression. The modifications were each known in the art, as evidenced by the modified antisense oligonucleotides and ribozymes taught by Pavco et al., modified siRNA duplexes taught by Elbashir et al. and Parrish et al., modified ribozymes taught by Matulic-Adamic et al., and modified oligonucleotides taught by Cook et al. One would be motivated to maximize a double stranded nucleic acid by incorporating each of the modifications that were known in the

art. Elbashir et al. and Parrish et al. each teach combinations of modifications to duplexes and teach that different modifications are tolerated at different locations of the duplex. One would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a dsRNA duplex in order to optimize delivery of the duplex.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to oligonucleotides. One would expect for such modifications to benefit siRNA duplexes, as each had shown to benefit other oligonucleotides such as antisense oligonucleotides or ribozymes. One would reasonably expect for polynucleotide or non-nucleotide linkers as taught by Matulic-Adamic et al. to benefit the instant invention since such linkers were known in the art at the time the invention was made.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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